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Document Number:

11) IV-E-6

Docket Number:

A-90-16

A-90-16
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UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

OFFICE OF
AIR AND RADIATION

MEMORANDUM

SUBJECT: Meeting with Representatives of Ethyl Corporation

FROM: David J. Kortum, Environmental Engineer
Field Operations and Support Division (EN-397F)

TO: Air Docket (LE-131)

David J. Kortum 10/22/90

On October 2, 1990, two meeting were held between representatives of EPA and the Ethyl Corporation regarding Ethyl's request to use MMT in unleaded gasoline. Those present at the first meeting from EPA included: William Rosenberg, Tom Kiernan, Karen Levy, Richard Wilson, Mary Smith, David Kortum, Nancy Ketcham-Colwill and Dwight Atkinson. Representatives of Ethyl Corporation included: Jeffrey Smith, Gary Ter Haar, Cindy Langworthy and Bill Brownell. Jeffrey Smith presented a brief overview of Ethyl's request to use MMT in unleaded gasoline. General Smith also indicated that Ethyl would be providing some vehicles from their test fleet to EPA's Motor Vehicle Emissions Lab in Ann Arbor Michigan for testing. Subsequent discussion centered around issues associated with catalyst durability and manganese inhalation. Ethyl indicated that further docket submissions would be forthcoming.

Those present at the second meeting included (from EPA): Erich W. Bretthauer, John Skinner, Michael Winer, Peter Preuss, Karen Levy, Stan Durkee, William Farland, Robert Fegley, Dwight Atkinson, Mary Smith and David Kortum. Attendees representing Ethyl Corporation included: Jeffrey Smith, Gary Ter Haar, Bill Brownell, and Cindy Langworthy. Jeffrey Smith presented a brief overview of Ethyl's request to use MMT in unleaded gasoline. Subsequent discussion centered around health issues related to manganese exposure through inhalation. EPA representatives indicated that microenvironment exposure to manganese from vehicle emissions may be an important consideration and also suggested that, among a population, there may be a distribution of exposures. Ethyl representatives pointed out that it was their view that the issue of manganese inhalation exposure was a relatively new issue which had not been stressed prior to their application for a waiver.

I have attached a copies of handouts which were distributed by Ethyl representatives at these meetings.

Attachment

Manganese: Inhalation vs. Ingestion

I. The Contribution of Inhaled Manganese to Daily Intake is Very Small

As stated by Dr. H. Daniel Roth:

"It is important to recognize that inhaled manganese contributes very little (less than 1%) to the total daily intake of manganese [see Attachment A]. Assuming an ambient manganese concentration of 0.03 ug/m^3 and an adult ventilation rate of 20 m^3/day, we find that inhalation contributes only 0.6 ug/day (0.0006 mg/day). The average manganese intake for an adult is approximately 3.31 mg; thus inhaled manganese contributes only .018 percent of the total manganese intake. [Conservatively, total manganese intake from inhalation associated with use of the Additive would, at most,] represent[] an increase of 0.0544 percent .... Considering that manganese is an essential nutrient, such a minor increase in daily intake cannot be considered a health threat."

II. There is No Credible Evidence which Shows that Inhaled Manganese Accumulates More Readily in the Central Nervous System than Manganese from Ingestion or Other Routes of Exposure.

As stated by Dr. Carl Schulz, Ph.D, DABT:

"[The National Institute of Environmental Health Sciences ("NIEHS")] speculates, without evidence, that MMT is readily absorbed "via the nose" and that this might result in higher levels of manganese in the CNS than comparable doses by other routes. As stated above, the manganese is emitted in engine exhaust as inorganic oxides, mostly presumably in particulate form. Depending on particle size, a significant but unknown proportion of the manganese that enters the respiratory tract will deposit on the surface of the upper respiratory tract and will be expelled or cleared to the gastrointestinal tract by normal mucociliary clearance mechanisms. There is no evidence, and it is unlikely, that a significant amount of manganese will be absorbed through the mucosa of the nasopharyngheal region of the upper airway. In any event, this does not guarantee ready access to the brain. Absorption would occur into the general circulation and the blood supplying the capillary bed of the nasopharyngheal mucosa must pass back through the heart, lungs, and probably the kidneys and liver before it reaches the brain. There is no shortcut from the nose to the brain as implied .

[NIEHS also] points out that most of the toxicity data are by the oral route of administration and do not apply to other routes. This generalization applies only to experimental studies. There is a large body of health effects information derived from studies of workers who are occupationally exposed to manganese compounds almost exclusively by the inhalation route (see HEI 1988, Cooper 1984, EPA 1984, and WHO 1981 for reviews of these studies)."

As stated by Dr. Robert Lauwerys, MD, MIH, Dsc:

"For the general environment, WHO ... has recommended an annual average of 1 ug manganese/m^3 as a guideline value. This value should incorporate a sufficient margin of safety for the most sensitive population group."

It's Time For Americans To Reap The Benefits Of HiTEC 3000 Performance Additive

Ethyl has shown that use of the additive will have these benefits:

- Reduce NOx and CO tailpipe emissions
- Have no practical, adverse effect on HC emissions
- Enable a reduction of the aromatic content of unleaded gasoline
- Facilitate compliance with tightened gasoline volatility standards
- Reduce total pollutant emissions by 1.7 billion pounds annually by 1999
- Potentially reduce ambient ozone concentrations in some cities
- Save more crude oil annually than is purchased each year for the Strategic Petroleum Reserve
- Be compatible with gasolines containing oxygenates, methanol or ethanol
- Cause no damage or deterioration of automobile emission control systems
- Cause no health or environmental problems

Overall Tailpipe Emissions Are Reduced By 8 Percent

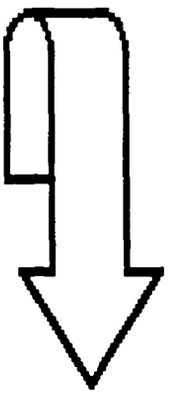
The additive reduces overall tailpipe emissions by 8 percent. In 1999, Ethyl estimates that total annual emissions will be reduced by nearly 1.7 billion pounds as cars with advanced emissions technology comprise the majority of the fleet in the United States.

TOTAL POLLUTANT REDUCTION

USE OF HiTEC® 3000 PERFORMANCE ADDITIVE

(pounds per year)

Pollutant	1999
Nitrogen Oxide	644,000,000
Carbon Monoxide	988,000,000
Hydrocarbons*	0
Particulates	1,100,000
Sulfur Oxides	150,000
Aromatics	35,200,000
Formaldehyde	3,500,000
Total	1,671,950,000

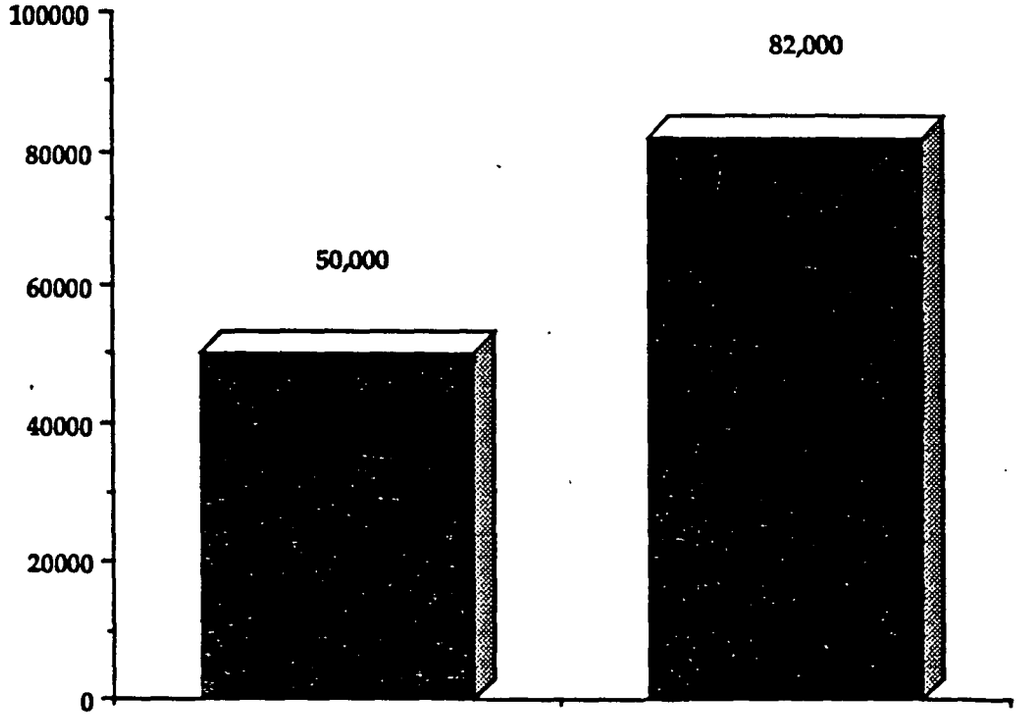


*assumes use of HiTEC® 3000 performance additive replaces aromatics in commercial fuel

Refineries Will Be Able To Operate Under Less Severe Conditions

Since the additive raises octane up to one octane number, refineries are able to reduce processing "severity" and thereby reduce the amount of crude oil needed. Experts estimate that crude oil imports could be reduced by 30 million barrels per year if the additive were used in unleaded gasoline. That would create a potential reduction in the U.S. trade deficit of between $500 million and $1 billion a year. The 30 million barrels saved would be more than the amount of oil stored annually in the Strategic Petroleum Reserve.

HiTEC® 3000 AND SAVINGS IN CRUDE OIL



MANGANESE AND PUBLIC HEALTH

(Re: Ethyl Waiver Application for HiTEC 3000)

September 21, 1990

I. Manganese Is A Common Element Essential For Human Life

- Normal daily intake of manganese ranges from 2,000 to 9,000 micrograms, averaging about 3,000 micrograms. On June 19, 1990, the Food and Drug Administration proposed a recommended daily intake of 3,500 micrograms of manganese for adults.

- The maximum intake of manganese after 70 years of use of the Additive would be less than two micrograms per day (ingestion and inhalation) compared to intake from one daily multivitamin tablet (1,000-10,000 micrograms), one cup of tea (1,200 micrograms) or a slice of whole wheat bread (334 micrograms).

- The cumulative concentration of manganese in soil at a point 5 meters from a busy expressway caused by 50 years of use of the Additive would be less than the concentration caused by spilling one cup of tea, one time, at that point (4.6 versus 6.9 parts per million).

- After 50 years of use, the cumulative contribution of the Additive to manganese concentrations in soil 5 meters from a busy expressway would be the same as that resulting from watering one's lawn once per year (with a normal watering rate of 1 inch) during this period.

II. Recent EPA Sponsored Documents Relating To Manganese

1984: EPA released a comprehensive "final report," titled "Health Assessment Document for Manganese" in August 1984. The report was subjected to a peer review. The document's findings were endorsed by the EPA Science Advisory Board. Among other things, the document (p. 6-23) stated that the lowest observed effect level (LOEL) of manganese for neurological problems was 300 micrograms per cubic meter of air (300 ug/m^3).

1985: The EPA (in the Federal Register, Vol. 50, No. 156, 13 August 1985, pp. 32627-8) announced a "decision not to regulate manganese under the Clean Air Act" based upon the findings of the Health Assessment Document for Manganese. The EPA notice stated that (1) "present ambient air concentrations of manganese do not pose a significant risk to public health; (2) public exposure to manganese is presently far below any level associated with non-carcinogenic serious health effects; (3) evidence currently available does not indicate that manganese is carcinogenic."

1986: The Health Effects Institute (HEI, 215 First Street, Cambridge, MA -- an independent scientific body jointly funded by EPA and automobile manufacturers) published a study, requested by EPA, titled "Potential Health Effects of Manganese in Emissions from Trap-Equipped Diesel Vehicles." Among other things, the HEI report stated that:

- EPA had derived manganese levels ranging between 5 and 36.5 ug/m^3 below which there would be no observed respiratory effects (p. 26).

- It was "unlikely" that adverse health effects (neurological or respiratory) would occur at a manganese emission level of 0.5 ug/m^3 of ambient air. The 0.5 level is, conservatively, ten times higher than that which would result were HiTEC 3000 (MMT) used (at a concentration of 1/32 gm/gallon) in all U.S. unleaded gasoline.

BOTTOM LINE: Conservatively, the use of HiTEC 3000 (MMT) in all U.S. gasoline would cause no more than a 0.017 ug/m^3 increase of manganese in ambient air. That, in turn, would cause a total, average manganese level of no more than 0.05 ug/m^3 -- 100 times less than the lowest of the observed respiratory effect levels (5 to 36.5 ug/m^3) derived by EPA -- and 6,000 times less than the lowest observed neurological effect level (300 ug/m^3) cited by EPA in the Health Assessment Document.

III. Studies and Authorities Supporting No Adverse Health Effects From Use of the Additive

- The Canadian Department of National Health and Welfare concluded in 1978 that "there is no evidence at present to indicate that expected ambient manganese concentrations [from automobile exhaust] would constitute a hazard to human health."

- In 1986, the Royal Society of Canada again reviewed the health literature and concluded that "the general public has a wide margin of health safety with respect to the worst case use of MMT in gasoline."

- In 1987, an official from Australia's Department of Health concluded that "there is no toxicological evidence to suggest that the increased level of airborne Mn resulting from combustion of MMT as a petrol additive is likely to constitute a health risk to the general population."

- The World Health Organization in 1987 concluded that an annual average concentration of 1 ug/m^3 -- about ten to one hundred times higher than maximum urban ambient concentrations associated with use of the Additive -- "incorporates a sufficient margin of protection for the most sensitive population group."

- In a letter of July 17, 1990 to the docket in this proceeding, Environment Canada stated: "Health and Welfare Canada has evaluated the possible health effects of using MMT in gasoline. That department has advised Environment Canada there would be no significant increase of manganese in the environment to affect public health by the use of MMT in gasoline."

- A 1990 review and assessment of the health literature on manganese by Roth Associates, a firm staffed by experts in toxicology and epidemiology who have served on EPA scientific advisory panels: "None of the concerns raised by commenters provide a sound basis for concluding that the addition of MMT to gasoline as proposed by Ethyl would endanger public health. In conclusion, we have found that use of MMT is unlikely to affect public health adversely. The anticipated increase of manganese in the environment from use of MMT is sufficiently small in comparison to the natural levels of this element and human intake of it that the body's ability to maintain consistent manganese levels should be unaffected."

- Dr. Henry M. Wisniewski (neuropathologist, expert on aging process, Director of Institute for Basic Research of N.Y. Department of Health): "Ethyl provided enough evidence to show that adding manganese will not negatively affect human health and environment. . . . There is no evidence to suggest that [neurotoxic] effects take place at lower Mn levels . . . [The evidence] is clearly in favor of approving Ethyl's application."

- Dr. Robert Lauwerys (Professor of Industrial Toxicology and Occupational Medicine, Director of the Unit of Industrial Toxicology and Occupational Health at University of Louvain, Brussels): [The World Health Organization's recommended guideline of 1 ug/m^3 average manganese exposure] "should incorporate a sufficient margin of protection for the most sensitive population group." (Note: The Additive would result in ambient manganese levels 10 to 100 times less than 1 ug/m^3.)

- Dr. W. Clark Cooper (former Medical Director of U.S. Public Health Service): Following a 1984 comprehensive review of then-existing literature on public health implications of manganese in the environment, he concluded that the "minute increments of Mn that would result from the use of MMT as a gasoline additive should not have any impact on the public's health." Following a recent review of available literature, he stated that "[A]s of July 1990, I am not aware of any new evidence to alter the conclusions [of the 1984 review]; if anything they have been strengthened."

MANGANESE AIR LEVELS

(Re: Ethyl Waiver Application for HiTEC® 3000)

October 1, 1990

I. MANGANESE AMBIENT AIR LEVELS

(micrograms per cubic meter, ug/m^3)

- Toronto 1985-1987 .027-.045 ug/m^3
- New York City (Bronx) 1968-1982 .029-.054 ug/m^3
- Total U.S. 1980-1982 .030-.033 ug/m^3

II. CONCEIVABLE NET MANGANESE AIR LEVELS IN THE UNITED STATES, ASSUMING USE OF MMT, AND BASED UPON --

	Increase (I)	Net Level (I + .033)
• "Origins of Manganese in Air Particulated in California," Journal of Air Pollution Control Assn. (1988)	.003-.013	.036-.043 ug/m^3
• Conservative Estimate of 30-35% Mn becoming airborne	.017	.05 ug/m^3
• Quite Unlikely Estimate of 75% Mn becoming airborne	.043	.076 ug/m^3

III. NOTE THAT --

- Urban Toronto manganese air levels, where MMT has been used in virtually all unleaded gasoline at twice the requested U.S. concentration, average well below .05 ug/m^3.
- The World Health Organization, in 1987, concluded that 1 ug/m^3 was a safe level for manganese in ambient air for the most sensitive population.
- EPA's "Health Assessment Document for Manganese" (1984-85) states that 300 ug/m^3 is the lowest observed effect level of manganese for neurological problems and that "data available for identifying effect levels below this level is (sic) equivocal or inadequate."
- The Health Effects Institute, in a 1986 study for EPA, stated that EPA derived manganese levels for no observed respiratory effects ranged from 5 to 36.5 ug/m^3.
- EPA's 1985 review of the "Health Assessment Document for Manganese" concluded that manganese exposures as high as 250 ug/m^3 for 15 minutes and 125 ug/m^3 for 8 hours were "well below the protective levels" established by the NAAQS for particulate matter and by the World Health Organization and American Conference of Governmental Industrial Hygienists for neurotoxic effects.

IV. BOTTOM LINE:

In the quite unlikely circumstance of 75% of the manganese burned in the automobile fuel becoming airborne, it would still result in exposure levels far, far below those deemed safe.

1 October 1990

Brain Uptake of Manganese Following Exposure by Inhalation

(Prepared Re Ethyl Waiver Application for HiTEC 3000)

Carl O. Schulz, Ph.D., DABT

I have been asked to address the issue as to whether exposure to manganese (Mn) by inhalation results in greater uptake and higher brain levels of Mn than does exposure by the oral or dermal routes. Based on my experience and review of the available literature, I have concluded that there is no evidence that inhalation results in greater absorption of Mn or preferential distribution to the brain compared to oral exposure. Furthermore, there is no reliable evidence that Mn accumulates in the brain or that inhalation enhances accumulation. The available evidence indicates that the uptake and elimination of Mn following inhalation exposure is dependent upon the solubility and the particle size distribution of the Mn compounds in the respired air. Furthermore, homeostatic mechanisms that control the body burden (including brain levels) of Mn appear to operate independently of the route of exposure.

Airborne Mn is almost entirely in the particulate form and is predominantly insoluble oxides. Upon inhalation it behaves like all insoluble particulates. Depending on particle size, some of it will deposit in the upper airways where it can be expelled through sneezing and coughing or swallowed with mucous, entering the G.I. tract. Some small but unknown fraction may be absorbed through the mucous membranes lining the upper respiratory tract. Particles having a sufficiently small diameter will enter the lower airways and the alveoli. Some of these will deposit on the airway or alveolar walls while others will remain suspended and be exhaled. Particles depositing on the walls of the lower airways may be absorbed or may be cleared to the G.I. tract by mucociliary action. Particles depositing in the alveoli will eventually be absorbed into the systemic circulation. Thus, an unknown, but likely small, fraction of inhaled manganese is absorbed through the lungs with the remainder being exhaled or transferred to the G.I. tract. The distribution among these is determined by particle size. Mena et al. (1969) reported that a large percentage of the $MnCl_2O_2$ to which humans were exposed in their study was absorbed by the G.I. tract.

There is almost no information in the scientific literature on concentrations of Mn in the brains of humans who have been exposed to manganese or who exhibit signs and symptoms of Mn intoxication. What little information is available is contradictory. Banta and Markesbery (1977) reported that brain Mn levels were three times normal levels in a man suffering from Mn poisoning as a result of self-administration of drugs containing high levels of Mn. In a follow-up study, one of these authors and coworkers measured the brain Mn concentrations in 14 patients with Alzheimer's disease and in 33 non-demented individuals of various ages (Markesbery et al. 1984). They found no significant differences in Mn levels between AD patients and the controls and they found no increase of brain Mn levels with age, leading them to conclude that the brain has an efficient homeostatic mechanism regulating Mn concentrations. Yamada et al. (1986) measured the concentration of Mn in the brain of a 52-year old man suffering from chronic manganese poisoning and found no significant difference in either the concentration or the distribution of manganese in the brain compared to controls. Borit et al. (1975 as cited in Bleecker 1988) found elevated Mn levels in the brains of patients afflicted with a disease known as striatonigral degeneration. Taken together, the human evidence, while limited, does not support any conclusions regarding correlations between levels of Mn in the brain and either exposure or disease.

Studies in experimental animals provide no support for the hypothesis that exposure to Mn by inhalation leads to higher levels of Mn in the brain than does exposure by other routes. Mouri (1973, as cited in Cooper 1984)) compared the absorption and distribution of MnO_2 dust after oral and inhalation exposure in mice. Mice were exposed to air concentrations of 8.91 and 5.55 mg/m^3 Mn for 2 hours per day for 8 and 15 days respectively. Levels of Mn in various tissues were compared to those in tissues of mice receiving comparable oral intakes of Mn. While Mn levels in the lung, trachea, and G.I. tract were much higher in the mice exposed by inhalation than in mice exposed orally, Mn levels in other tissues were only slightly higher in mice exposed by inhalation. Thus, the ratio of Mn concentrations in the brain for inhalation and orally exposed mice was 1.3. It appears from these results that mice are able to regulate body burdens of Mn regardless of the route of exposure. It should be noted that the air concentrations to which these mice were exposed were in excess of the current ACGIH TLV for Mn dust and compounds and

exceed the upper limit estimate of airborne Mn concentrations that might be associated with the use of MMT in gasoline by a factor of more than 50,000.

Morganti et al. (1985) exposed young adult male mice to MnO_2 dust for 7 hours per day, 5 days per week. The exposed animals were observed for signs of overt toxicity and tested for alterations in behavioral and learning performance. Animals were sacrificed at 4-week intervals from 16 to 32 weeks of exposure and 4 weeks after exposure ended and tissue levels of Mn were measured. The concentrations of airborne manganese to which the mice were exposed were measured at 49.1 mg Mn/m^3 for the first 12 weeks and at 85.3 mg Mn/m^3 for weeks 13 through 32. The mass median diameter of the MnO_2 particles was 1.5 um. These concentrations exceed the current ACGIH TLV for manganese dust and compounds by a factor of from 10 to 17. They are also more than 500,000 times higher than the upper limit estimate of ambient airborne manganese concentrations that might possibly result from the use of MMT in unleaded fuel.

Tissue level measurements indicated that manganese levels were significantly higher in all tissues, including the brain in the exposed animals after 16 weeks of exposure, compared to the sham-exposed control animals. However, from weeks 16 to 32 the manganese levels of all tissues except the liver decreased in the exposed animals and after 32 weeks were not different from tissue levels in the control animals. No gross toxicological effects were observed in the exposed animals but there were subtle differences between exposed and control animals in some, but not all, of the behavioral assessments.

The authors concluded that after an initial increase in tissue manganese levels during the early weeks of exposure, the liver controls the body burden of manganese by concentrating manganese for biliary excretion, and this mechanism serves to regulate tissue levels of manganese even at the excessive airborne exposure levels in this study.

Drown et al. (1986) studied the uptake and elimination of radiolabelled $MnCl_2$ and Mn_3O_4 after intratracheal administration to adult male Sprague-Dawley rats. Their results indicated that the soluble form ($MnCl_2$) was taken up and excreted more rapidly than the insoluble form (Mn_3O_4). Concentrations of Mn in the

brain peaked one day after administration of $MnCl_2$ and 3 days after administration of Mn_3O_4. Levels of Mn in the brain decreased after 2 weeks and fell off sharply after 60 days. These results indicate that Mn absorbed through the lungs is not sequestered irreversibly in the brain.

Newland et al. (1987) studied the clearance of Mn from various body regions in monkeys who were given acute doses of radiolabelled $MnCl_2$ by intratracheal installation. Estimated doses of 0.01 - 0.02 ug of radiolabelled $MnCl_2$ were administered to two female monkeys using an endotracheal tube connected to a respirator for approximately 30 minutes. They then monitored radioactivity in the chest area, the head and in the feces for over a year. They found that radioactivity in the head area decreased at a slower rate than did radioactivity in the chest area, leading them to conclude that "long-term exposure to even low levels of manganese will cause significant accumulation in the brain." This conclusion must be considered to be purely speculative, however, in light of the limited nature of the data that they presented. First, the method used to determine the levels of radioactivity in the various regions of the body could not determine in which organs or tissues the radioactivity was localized within those general areas. Thus, the total radioactivity in the head region may include radiolabelled Mn in the blood, hair, and skin as well as in the brain. Second, the authors failed to differentiate between the kinetics of Mn turnover in the head region and mass balance. Slower turnover of Mn in the head compartment is not sufficient, by itself, to indicate accumulation which can only be determined by measuring the concentrations of total Mn in the brain. Finally, the authors noted that the slower rate of decline of radioactivity in the head area probably reflects replenishment of Mn in that compartment from radiolabelled Mn deposited in other organs. Radioactivity in the abdominal region (liver, kidneys, spleen, G.I. tract) and in the whole body were not determined in this study. The apparent retention of radioactivity in the head may very well have been secondary to the release of radiolabelled Mn from some other storage depot. In view of these limitations and the fact that the study involved the acute administration of a soluble Mn compound to only two animals, it cannot be considered to be evidence for the authors' speculative conclusion that inhalation of Mn may lead to brain accumulation.

Finally, it should be emphasized that in the most relevant animal study conducted to date, there were few signs of toxicity and no histopathological evidence of tissue damage in rats and monkeys exposed by inhalation to up to 1.15 mg/m^3 of Mn_3O_4 prepared by the combustion of MMT 24 hours per day for 9 months (Ulrich et al. 1979). Unfortunately, these authors did not measure Mn concentrations in the brains of exposed animals. However, they did measure Mn concentrations in the blood, lung, liver, kidneys and spleen. The study found that while lung levels were significantly elevated at all exposure levels, Mn levels in the blood and spleen were elevated only at the highest dose, and liver levels were not increased at any dose level. This indicates that Mn levels in the body are homeostatically controlled regardless of the route of exposure.

In conclusion, the data available from studies in experimental animals exposed to concentrations of airborne manganese far higher than any likely to result from the use of MMT as a gasoline additive do not show significantly increased uptake, accumulation (including in the brain), or toxicity when compared to animals exposed to similar doses by the oral route. Only a small fraction of inhaled Mn is absorbed through the lungs with the remainder passing to the G.I. tract or being expelled in the expired air. Body burdens of Mn after exposure by inhalation seem to be controlled by the same mechanism (primarily increased biliary excretion in the liver) that serves to control Mn body burden after exposure by any other route.

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